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ART UNIT	**PAPER NUMBER**
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/688,821	WICKSTROM ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2008*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3,4,7-14,16,26-34,41-45,48-52,54-56,69-73,75,80-83,86 and 88-101.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/2008 has been entered.

Claims 2, 5, 6, 15, 17-25, 35-40, 46, 47, 53, 57-68, 74, 76-79, 81, 84, 85, and 87 have been cancelled. Claims 1, 3, 10, 16, 82, 88, 89, and 93-95 have been amended.

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 are pending and under examination.

2. The following rejections are withdrawn in favor of revised rejections using a combination of references which provide a better motivation to arrive at the instant invention:

The rejection of claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, 89-95 under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180), in view of both Liang et al. (Molecular Therapy, 2000, 3: 236-243, of record) and Basu et al. for the reasons of record set forth in the non-final Office action of 07/26/2007.

The rejection of claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-95 under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of Nakano et al.

The rejection of claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, and 88-95 under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of both Tomalia et al. and Meade et al.

Claim Rejections - 35 USC § 112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the first three lines claims 1, 88, and 89 recite that the therapeutic moiety is directly associated with the targeting moiety and with the PNA (i.e., P-X-T) and later the claim recites that the therapeutic moiety is indirectly associated with the targeting moiety via PNA (i.e., X-P-T). Since it is not clear what arrangement is claimed, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 90-101 are rejected for being dependent from the rejected claim 1 and also for failing to further clarify the basis of the rejection.

For examination purposes, the claims are interpreted as being drawn to a compound with the formula X-P-T.

Claim Rejections - 35 USC § 112, 1st paragraph – new matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendments to the claim to include the term a therapeutic or diagnostic agent covalently conjugated to a targeting moiety (claims 1, 88, and 89) and "Fe(III), Eu(III)" introduce new matter.

Applicants point to paragraph 0047 of the published application as supporting the amendment to claim 1, 88, and 89, and to paragraph 0065 as supporting the recitation

of "Fe(III), Eu(III)". It is noted that the indicated paragraph 0047 recites a diagnostic moiety comprising a dendrimer conjugated to diagnostic compounds; there is no recitation of the diagnostic moiety being directly conjugated to a targeting moiety. The indicated paragraph 0065 discloses linkers and not diagnostic compounds. It is noted that paragraph 0048 does recite Fe and Eu however, there is no recitation of "Fe(III) or Eu(III)". Fe and Eu could also be divalent and the general recitation of Fe and Eu does not provide support for the specific selection of Fe(III) and Eu(III). A search of the remaining portions of the specification failed to provide literal support for such recitations.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. (US Patent No. 5,714,166, of record), in view of both Basu et al. (Bioconjugate Chem, 1997, 8: 481-488, of record) and Meade et al. (US Patent No. 6,713,046, of record).

Tomalia et al. teach a compound having the formula T-P-M, wherein P represents a dendrimer such as PMAM (i.e., polymeric diagnostic or therapeutic moiety, which is a branched oligomeric polychelant) or Starburst, M represents a carried material such as PNA, T represents a targeting moiety that can be an antibody fragment such as Fab, Fab', and wherein M and T are associated with the dendrimer via the same or different linkers (i.e., covalent bond); the linkers could be cleavable (claims 1, 4, 7-10, 34, 88, 89, and 99-101) (column 1, lines 45-50, column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60). Tomalia et al. teach that two or more dendrimers can be associated with each other (covalently bridged or through other associations) (claim 12) and that the dendrimers can comprise chelants, i.e., the diagnostic moiety comprises a plurality of chelants,

wherein the chelants can be complexed with diagnostic metal ions (claims 13 and 26) (column 3, lines 22-40, column 13, lines 5-11, column 19, lines 11-16, column 22, lines 1-29, column 45, lines 1-9,) and optionally can comprise additional agents that could be diagnostic metal ions, such as gadolinium (claims 4, 13, 14, 16, and 54) (column 1, lines 59-65, column 22, lines 15-35, column 88, Example 24, column 89, Table XI). Tomalia et al. teach that the compound can be used either *in vitro* or *in vivo* as a cancer therapeutic and diagnostic agents for noninvasive imaging and for transferring of genetic material, such as PNA into cells to block the production of specific proteins, i.e., Tomalia et al. teach a method of retaining a compound inside the cells for diagnostic or therapeutic purposes (claims 41-45, 48, 52, 69, 70, 73, 75, 90, 91) (column 28, lines 28-40, column 39, lines 25-30, column 54, lines 8-18, claim 32). For *in vivo* use, the compound can be administered into the portal vein, i.e., intravascular administration (claims 55 and 56) (column 54, lines 10-15). With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition, the transfection buffer (i.e., a pharmaceutically acceptable carrier) comprising the conjugate is a pharmaceutical composition (claims 83, 86, and 92). With respect to the specific linkers and their length (claims 1, 3, 88, 89, and 93-98), the specific chelants (claims 26 and 27), or the specific PNA lengths (claim 29), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method (in the instant case,

the linkers or the chelants) with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA (claims 30, 31, 50, 51, 71, 72, and 80), these are inherent to a method using PNA. It is noted that Tomalia et al. do not teach the specific arrangement X-L1-P-L2-T recited in the instant claims. However, Tomalia et al. teach all components necessary for this arrangement. It is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Although Tomalia et al. teach cleavable linkers, they do not specifically teach a biodegradation cleavage site. Meade et al. teach a biodegradation cleavage site (claim 11) (column 14, lines 20-30). It would have been obvious to one of skill in the art, at the time the invention was made, to include a biodegradation cleavage site, as taught by Meade et al, with a reasonable expectation of success. The motivation to do so is provided by Meade et al. who teach that such a site allows the drug (in the instant case,

the PNA) to freely interact with its target. One of skill in the art would have been expected to have a reasonable expectation of success because Meade et al. teach the successful use of such sites.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" (column 47, lines 55-62). The other recitations of the (T)e*(P)x*(M)y structure (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples. Therefore, Applicant argues, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers. Furthermore, Applicant argues that Tomalia et al. actually teach a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52; column 18, lines 23-67; column 19, lines 1-67; column 20, lines 1- 29; column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds. Applicant submits that the L1 and L2 spacers are a non- obvious solution, not taught or suggested

by Tomalia et al., or the combination of the references, to the problem of steric hindrance between the three functional units of the claimed compound. In addition, the claims are directed to spacers of from 10Å - 30Å, which is not taught or suggested in the Tomalia reference. This deficiency is not cured by the Basu or Meade references. Additionally, as noted above, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers. Applicant also argues unexpected results as shown in the Declaration under 37 CFR § 1.132 of Dr. Eric Wickstrom, submitted December 19, 2007. Applicant notes that the Examiner attempts to argue that Tomalia can be modified with Meade and Basu to arrive at the claimed invention. However, Applicant argues, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia. In fact, Applicant had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Here, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. This is shown here. With regard to the Declaration, Applicant notes that the Examiner also argues that the specification teaches that dendrimers can be prepared such that they have reactive groups capable of being attached to a variety of compounds including PNA and linkers and that techniques of attaching PNA to the dendrimers are within the skill in the art and concludes that the Declaration is not consistent with the teachings in the specification. (Final Office Action at page 8).

However, as shown in the Declaration, Applicants' attempt to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, as in the In re Ratti case, therefore the claims are patentable. In addition, Applicant argues, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see In re Rinehart, 531 F.2d 1048 (CCPA 1976), MPEP 2143.02. Here, Applicant attempted to use Tomalia's teachings as the basis for reaching the claimed invention, but was unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

Applicant's arguments are acknowledged however, they are not found persuasive for the following reasons:

Applicant argues that at no point do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer. Such a statement is inaccurate. Tomalia et al. teach a compound with the formula (T)e*(P)x*(M)y wherein M represents a diagnostic or therapeutic agent, T represents a targeting moiety, and P represents a dendrimer; M could be associated with the dendrimer via a covalent bond and M could be a nucleic acid such as PNA (column 17, lines 40-65; column 20, line 12; column 21, lines 27-33; column 22, lines 15-25). Therefore, Tomalia et al. do not teach away from

covalent bonding of genetic materials to dendrimers and Basu or Meade references have nothing to remedy. Applicant states that the L1 and L2 spacers are a non-obvious solution, not taught or suggested by Tomalia et al., or the combination of the references, to the problem of steric hindrance between the three functional units of the claimed compound. This statement is incorrect because Tomalia et al. do teach that the linkers are used to avoid steric hindrance (column 17, lines 40-60). Applicant argues that the proposed modification or combination of the prior art changes the principle of operation of the prior art invention being modified. Such is just an argument not supported by any evidence. The purpose of Tomalia et al. is obtaining a composition suitable for targeted delivery. Modifying the arrangement as indicated above does not change this, i.e., the modified composition would still be suitable for targeted delivery. Applicant did not present any evidence to the contrary. The argument that Applicant was unsuccessful to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia is not found persuasive. An obviousness-type rejection is based on the knowledge available in the prior art as a whole. The prior art teaches how to successfully link dendrimers to nucleic acids nucleic acids via a covalent bond. For example, Goh et al. (Chem. Commun., 2002, 24: 2954-2955) teach solid-phase synthesis of covalent dedrimer-olignucleotide conjugates by linking dendrimers to oligonucleotides attached to solid supports (p. 2954 and 2955). Additionally, Basu et al. teach solid phase synthesis of targeting ligand-PNA conjugates, wherein the targeting ligand is automatically synthesized on a solid support, followed by the assembly of the PNA. Therefore, by reading Basu et al. and Goh et al., one of skill in the art would know

how to successfully extend a dendrimer from a solid phase-attached ligand-PNA. This is not different from the method presented in the Declaration, which method would have been available to one of skill in the art at the time the invention was made. Additionally, the prior art teaches the successful solid phase synthesis of targeting ligand-PNA conjugates (see Basu et al., p. 482, columns 1 and 2, Fig. 2). Therefore, one of skill in the art would know how and would have expected to be successful in modifying Tomalia et al. to arrive at the instant invention. The Declaration does not provide any evidence that this is not possible and moreover, the specification teaches that one of skill in the art would easily link a dendrimer to a ligand-PNA. For these reasons, Applicant's arguments of no reasonable expectation of success are not found persuasive. For all these reasons, the rejection is maintained.

9. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, and 88-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. (Molecular Therapy, 2001, 3: 491-499, of record).

The teachings of Tomalia et al., Meade et al., and Basu et al. are applied as above for claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-92. Tomalia et al., Meade et al., and Basu et al. do not teach an oncogene, wherein the oncogene is K-RAS (claims 32, 33, 72, and 82), nor do they specifically teach treating pancreatic cancer (claim 49). Nakano et al. teach gene therapy by using antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last

paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to use the compound and the method of Tomalia et al., Meade et al., and Basu et al., wherein the PNA is directed against K-*ras*, to deliver diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to over-express K-*ras*, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is over-expressed in many cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Nakano et al. do not cure the deficiencies of Tomalia et al., Meade et al., and Basu et al. The rejection is maintained because Tomalia et al., Meade et al., and Basu et al. do teach the claimed invention for the reasons set forth above.

10. Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180, of record), in view of Basu et al.

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety)

and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers (claims 1, 3, 4, 29, 31, 32, 34, 51, 52, 72, 73, 83, 86, and 89-97) (Abstract, p. 1177, Fig. 1). Lewis et al. teach contacting cells known to comprise high and low levels of *bcl-2* with the DOTA-PNA-peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of *bcl-2* transcript (claims 1, 30-32, 69, 71, 72, 80). Lewis et al. teach that cells expressing high levels of *bcl-2* internalize significantly more conjugate as compared to cells expressing low *bcl-2* levels, i.e., the presence of the conjugate inside the cells indicates over-expression of the *bcl-2* transcript therefore a pathological state that is cancer (claims 41, 42, 48-51, 75, and 80) (p. 1178, column 2 bridging p. 1179). It is noted that Lewis et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, Lewis et al. teach all components necessary for this arrangement. It is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Lewis et al. do not teach a targeting moiety capable of binding to a cell surface molecule (claims 1, 41, 89, and 90). Basu et al. teach enhancing PNA delivery to cells by receptor-mediated endocytosis via coupling the PNA to ligands for cell surface receptors (Abstract; p. 481, columns 1 and 2; p. 482, column 1;p. 487, column 1, last paragraph). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the composition of Lewis et al. by replacing their peptide with the ligand of Basu et al. to achieve the predictable result of obtaining a composition suitable for the intracellular delivery of nucleic acids. With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition (claims 83, 85, 86, and 92), the transfection buffer comprising the conjugate is a pharmaceutical composition. With respect to the specific linkers and their length (claims 1, 3, 88, 89, and 93-98), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA (claims 30, 31, 50, 51, 71, 72, and 80), these are inherent to a method using PNA.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection.

Applicant argues that the peptide of Lewis et al. is a permeating peptide intended for universal intracellular delivery of the radiolabeled PNA is not a specific cell surface receptor targeting moiety as recited in the presently amended claims. With respect to the linkers, Applicant argues that such spacers have only been introduced into such PNA constructs by the Applicant. Accordingly, the combination of the references does not teach or suggest all the claim limitations.

Applicant's arguments are acknowledged however, they are not found persuasive for the following reasons:

It is noted that the instant rejection is an obviousness-type rejection and therefore, Lewis et al. do not have to teach each and every claim limitation. It is the combination of Lewis et al. and Basu et al. which teaches a composition comprising a ligand for a cell surface receptor. With respect to the linkers, beside an argument, Applicant did not provide any evidence that he was the first to introduce these linkers introduced into PNA constructs. It is noted that the use of linkers to inhibit steric hindrance between in PNA construct is taught by the prior art (see the teachings of Tomalia et al. above). Optimizing the linker type and their size only requires routine

experimentation. Accordingly, the combination of the references renders the claimed invention *prima facie* obvious.

11. Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in further view of Nakano et al.

The teachings of Lewis et al. and Basu et al. are applied as above for claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-97. Lewis et al. and Basu et al. do not teach K-RAS (claims 33 and 82). Nakano et al. teach gene transfer antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al. and Basu et al. by using a PNA directed against K-*ras* and use it in a method of delivering diagnostic and therapeutic agents to cancer cells over-expressing K-*ras*, such as colon and pancreatic cancer cells, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is over-expressed in many cancer cells, including pancreatic cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Nakano et al. do not cure the deficiencies noted above. The rejection is maintained for the reasons set forth above.

12. Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, and 88-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in further view of both Tomalia et al. and Meade et al.

The teachings of Lewis et al. and Basu et al. are applied as above for claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 88-97. The teachings of Tomalia et al. and Meade et al. are applied as above for claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 85, 86, and 88-92. Lewis et al. and Basu et al. do not teach a dendrimer or a plurality of chelants optionally complexed to one or more diagnostic metal ions, a biodegradation cleavage site, or intravascular administration (claims 7-14, 16, 26, 27, 43-45, 54-56, and 88). Tomalia et al. and Meade et al. teach these limitations (see above). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al. and Basu et al. according to the teachings of Tomalia et al. and Meade et al., with a reasonable expectation of success. One of skill in the art would have been motivated to use the dendrimers of Tomalia et al. because the art teaches dendrimers as being very efficient in delivering agents to cells. The motivation to use a plurality of chelants is also provided by Tomalia et al., who teach that such compounds can be used to deliver multiple agents to cells. The motivation to use a biodegradation cleavage site is

provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target. The limitation of intravascular administration is not innovative over the prior art. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful maker and use of such compositions. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Nakano et al. do not cure the deficiencies noted above. The rejection is maintained for the reasons set forth above.

Conclusion

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Goh et al. (Chem. Commun., 2002, 24: 2954-2955) was cited in response to Applicant's argument that it would not have been predicted that dendrimers could be successfully linked to nucleic acids. Specifically, the reference teaches that dendrimers can be successfully linked to nucleic acids.

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ileana Popa/
Examiner, Art Unit 1633